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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	29

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No.	Applicant(s)	
	08/812,393	SHERMAN ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *6-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s) _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 1-19-01, paper number 28, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/812393 is acceptable and a CPA has been established. An action on the CPA follows.

The amendment filed 11-30-00, paper number 25, has been entered. The arguments therein have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

Claims 1-21 are pending. Claims 6-21 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions. Election was made **without** traverse in Paper No. 20. Claim 1-5 are under consideration in the instant application.

Claim Objections

In claim 1, the "immunizing" step should read "immunizing a transgenic non-human mammal whose genome comprises a nucleic acid sequence encoding a human leukocyte antigen (HLA) operatively linked to a promoter, wherein said transgenic non-human mammal expresses the HLA on the surface of antigen presenting cells (APC), with a tumor associated antigen (TAA)

such that the TAA is recognized by cytotoxic T lymphocytes (CTL) of the transgenic non-human mammal such that TAA-specific, HLA-restricted CTL are obtained," to be more clear.

In claim 1, in the cloning or amplifying step, there are brackets within brackets which is confusing. For examination purposes, the step is being read as "cloning or amplifying said nucleic acid molecule encoding the TCR nucleotide sequence isolated from the HLA restricted CTL, and..." which deletes the phrase in the outermost brackets.

In claim 1, line 4, the phrase "selected from" should be "selected from the group consisting of".

In claim 1, the "recovering" step does not result in isolation of a nucleic acid molecule encoding a TAA-specific TCR as in the preamble. The claim should be directed toward and result in "isolating a nucleic acid sequence encoding at least one variable region of the α or β chain of a..." to provide a nexus between the body and the preamble of the claim. The specific language is suggested: A method of isolating a nucleic acid sequence encoding at least one α or β chain of a variable region of a mouse T-cell receptor (TCR) that is specific for a human tumor associated antigen (TAA)... ...isolating a nucleic acid sequence encoding at least one α or β chain of a variable region of a mouse TCR that is specific for the TAA

Specification

The specification is objected to because page 13, line 9, has two blanks. Blanks are improper and should be filled in with the appropriate information

The specification is objected to because page 8, line 3, recites "(reference)" but does not have a reference.

Applicants are reminded that addition of such information to the specification may result in a new matter rejection. Support for amendments should be pointed to by page and line number.

The description of Fig. 3 should begin "Fig. 3A and 3B show the complete nucleotide (SEQ ID NO:1) and deduced amino acid sequence (SEQ ID NO:2) of ...".

The primers in Fig. 6 are SEQ ID NO:3-42 as indicated in the description of Fig. 6. However, Fig. 6 should clearly indicate the SEQ ID NO of each primer by putting the correct SEQ ID NO next each primer.

Claim Rejections - 35 USC § 112

1. Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a preparing a nucleic acid molecule encoding a mouse T-cell receptor (TCR) which recognizes an antigen comprising: 1) administering the antigen to a transgenic mouse whose genome comprises a nucleic acid sequence encoding human HLA-A2 molecule wherein said mouse functionally expresses human HLA-A2 on the surface of antigen presenting cells (APC) resulting in presentation of the antigen on the surface of an APC in the context of an HLA-A2 molecule, 2) inducing a CTL response against the antigen, 3) isolating antigen-specific CTL from the mouse and 4) isolating the nucleic acid molecule encoding antigen-

specific mouse TCR using RT-PCR, does not reasonably provide enablement for preparing a nucleic acid molecule encoding a non-human HLA-restricted TCR specific for a TAA using any transgenic non-human mammal and any cloning or amplifying method as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 1 recites the limitation of a transgenic non-human mammal which is modified so as to express at least one human HLA antigen. The state of the art at the time of filing was and continues to be that the gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct and the site of integration required to obtain the phenotype of interest in a transgenic non-human mammal were unpredictable (Wall, Ebert and Overbeek, all of record; Wall, 1996, Theriogenology, Vol. 45, pages 57-68; paragraph bridging pages 61-62; Ebert, 1988, Mol. Endocrinology, Vol. 2, pages 277-283; page 277, column 2, lines 17-27; Overbeek, 1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98; page 96, last paragraph).

The specification teaches administering human HER/2neu and a hepatitis B virus (HBV) helper peptide to a transgenic mouse expressing human HLA-A2.1 (A.2.1/KbxCD8 or A2.1 transgenic mice; page 9, line 11). The specification does not teach any other transgenic non-human mammals expressing human HLA molecules. Given the differences in the expression of a transgene within a litter of transgenic mice and between transgenic mice and other non-human

mammals, taken with the mere reference to the transgenic mice provided in the specification, it would have required undue experimentation to extend the transgenic mice referred to in the specification to other human HLA molecules or to other non-mouse, non-human mammals. Therefore, claim 1 should be limited to transgenic mice.

Claim 1 recites obtaining any non-human TCR from the non-human transgenic mammal. This encompasses obtaining a rabbit TCR from mice for example. Applicants have only enabled obtaining a TCR specific for the species of transgenic non-human mammal receiving the antigen because applicants do not teach how to obtain a TCR of one species from transgenic non-human mammal of a different species. Therefore, claim 1 should be limited to obtaining mouse TCR.

Claim 1 recites a transgenic non-human mammal which is modified so as to express at least one human HLA antigen. The entire HLA molecule must be expressed on the surface of an antigen- presenting cell to be of use in the instant invention. In addition, a cell expressing only one human HLA molecule is not of use in the instant invention. The HLA molecules must be expressed to significant levels such that antigen recognition can occur and CTL that recognize the antigen can be generated. Without adequate levels of HLA expression and production of CTL that recognize the administered antigen, the transgenic non-human mammal claimed is of no use. Therefore, claim 1 should recite a limitation indicating that the APC of the non-human transgenic mammal express the human HLA protein on their surface to levels adequate to allow antigen presentation in the context of the human HLA protein.

Claim 1 recites the TAA are selected form the group consisting of Her-2/neu, RAS, p53, tyrosinase, MART, Gp100, Mage, Bage and MUC-1 which are HLA-A2-restricted antigens. The specification only teaches transgenic mice expressing human HLA-A2. Given the unpredictability in the transgenic art as discussed above and the teachings in the disclosure, it would have required one of skill undue experimentation to determine the parameters required to use any other HLA molecules with Her-2/neu. RAS, p53, tyrosinase, MART, Gp100, Mage, Bage, or MUC-1. Therefore, claim 1 should be limited HLA-A2-restricted tumor antigens and a transgenic non-human mammal whose genome comprises a nucleic acid sequence encoding HLA-A2.

Claim 1 encompasses administering p53 to induce a CTL response in the transgenic non-human mammal. However, Theobald (Dec. 1995, PNAS, USA, Vol. 92, pages 11993-11997) teaches that CTL recognizing naturally occurring tumors expressing p53 are not obtained because either p53 is not expressed on the surface of the tumor or the p53 protein is not expressed to adequate levels such that a CTL response against p53 is produced (page 11995, col. 1, first full paragraph). The only disclosed use for isolating TAA-specific TCR is to use the TAA-specific TCR to recognize tumors expressing the TAA. Furthermore, claim 1 requires that the TCR specific for the TAA is sufficient to lyse tumor cells having the TAA. Since a p53-specific TCR cannot be used to recognize tumors expressing p53, the p53-specific TCR do not lyse tumor as claimed. Deletion of p53 is suggested. Similarly, other tumor antigens that are not expressed on the tumor surface or that are expressed on the tumor surface but do not induce a CTL response

do not have an enabled use in the method as claimed because the resulting TCR isolated does not have an enabled use.

Applicants argue that Wall, Ebert and Overbeek do not support the unpredictability in the art of transgenics. Applicants argument is not persuasive. Wall, Ebert and Overbeek support the examiners position because they teach that the phenotype of transgenics cannot be predicted. It would have required one of skill undue experimentation to determine the parameters required to obtain adequate expression of any HLA molecule in any transgenic non-human mammal such that the HLA was expressed on the surface of APC or that the amount of expression would be adequate to present antigens that is useful in the method claimed.

Applicants argue that transgenic sheep and pigs were known in the art at the time of filing; therefore, applicants argue other non-human mammals are enabled. Applicants argument is not persuasive because the sheep and pigs did not express HLA on their APC to adequate levels such that antigen presentation would occur. Nor does the phenotype of one species indicate that other species will have the same phenotype. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins produced transgenic rats with hypertension caused by expression of a mouse *Ren-2* renin transgene (Mullins et al., April 5, 1990, Nature, Vol. 344, pages 541-544). However, transgenic mice expressing the mouse *Ren-2* renin transgene failed to develop human disease-like symptoms (Mullins et al., 1989, EMBO

Journal., Vol. 8, pages 4065-4072). Thus, it was unpredictable that sheep or pigs would have expressed HLA-A2 on APC's or that the amount of expression on APCs was adequate to induce a CTL response. Given the unpredictability in the art and the lack of correlation between the phenotype obtained in two different species, it would have required one of skill to obtain human HLA expression in species other than mice. Therefore, the claims should be limited to transgenic mice.

Applicants argue that other transgenic mice expressing HLA antigens were known in the art at the time of filing. Applicants argument is not persuasive. Taurog taught transgenic mice expressing HLA-B27 and Ito taught transgenic mice expressing HLA-DR4. Applicants have not provided the references for consideration, but none of the TAA claimed are HLA-B27 or HLA-DR4-restricted. Nor are any HLA-B27 or -DR4-restricted tumor antigens disclosed. Therefore, it would have required one of skill undue experimentation to determine how to use the transgenic mice of Taurog or Ito in the claimed invention because the transgenic mice of Taurog or Ito could not be used to isolate TAA that are HLA-A2 restricted. Therefore, the claims should be limited to transgenic mice expressing HLA-A2.

Applicants argue that transgenic mice are excellent reservoirs of HLA-restricted antigen-specific T cells as supported by Taurog and Kawamura who teach using transgenic rats expressing HLA-B27 and HLA-DR2, respectively, to isolate HLA-restricted antigen-specific TCR. Applicants argument is not persuasive. Taurog taught transgenic rats expressing HLA-B27 and Kawamura taught transgenic mice expressing HLA-DR2. Applicants have not provided the

references for consideration, but none of the TAA claimed are HLA-B27 or HLA-DR2-restricted. Nor are any HLA-B27 or -DR2-restricted tumor antigens disclosed. Therefore, it would have required one of skill undue experimentation to determine how to use the transgenic rat of Taurog or the transgenic mouse of Kawamura in the claimed invention because the transgenics of Taurog and Kawamura cannot be used to isolate TAA that are HLA-A2 restricted. Therefore, the claims should be limited to transgenic mice expressing HLA-A2.

2. Claims 1-5 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the "recovering" step does not result in isolation of a nucleic acid molecule encoding a TAA-specific TCR as in the preamble. The "recovering" step as written requires two steps which are: recovering CTL from the mouse and isolating tumor antigen-specific CTL populations *in vitro*. Therefore, the claim does not provide the appropriate logical flow of steps required to isolate nucleic acids encoding TCR specific for TAA from CTL as claimed.

Claim 1 remains indefinite because it is unclear from the phrase "encoding at least one of the variable regions of the α and β chains" whether applicants intend to claim at least one variable region which can be either α or β chain or whether applicants intend to claim at least one α chain and one β chain.

Claim 4 is indefinite because it is unclear if the PCR used to amplify said nucleic acid molecule further limits the "cloning or amplifying" step claim 1 or if it is a separate additional step.

Claim 5 is indefinite because it is unclear if applicants are claiming a primer selected from the group consisting of SEQ ID NO:3-42 or if the all of the primers set forth in SEQ ID NO:3-42 are required in the claim.

Claim Rejections - 35 USC § 103

3. Claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Man et al. (1994, J. Immunol., Vol. 153, pages 4458-4467) in view of Cole et al. (April 1995, FASEB Journal, Vol, 9 page A801, abstract 4638) for reasons of record.

Man teach immunizing transgenic mice expressing HLA-A2.1 with the influenza A antigen, $M1_{(58-66)}$, isolating CTL from the mice that lyse the M1, amplifying the nucleic acid molecule encoding the α and β chain of the M1-specific TCR by PCR (page 4459, column 1, "influenza-specific CTL from HLA-A2.1 transgenic mice"; page 4459, column 2, "PCR amplification and sequencing of TCR α- and β-chain cDNA). The primers used by Man were mouse α and β TCR-specific primers Vβ8, Vβ5 and Vβ6 which are the primers Vβ8.1, Vβ8.2, Vβ8.3, Vβ5.1 and Vβ6 primers in Fig. 6. Man does not teach using the transgenic mouse to isolate TAA-specific TCR. However, at the time of filing a number of tumor associated antigens which were HLA-A2 restricted were known in the art at the time of filing and could have replaced

the $M1_{(58-66)}$. Cole taught MART-1 is recognized by CTL in an HLA-A2 restricted manner and taught generating MART-1-specific, HLA-A2 restricted CTL and isolating the TCR gene from the CTL (see entire abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of isolating TCR genes from transgenic mice taught by Man to obtain TCR genes specific for the MART-1 antigen. Motivation to isolate TAA-specific TCR genes from TAA-specific CTL is provided by Cole by teaching obtaining CTL which are specific for MART-1 and isolating the TCR receptors which are specific for MART-1. One of ordinary skill would have been motivated to replace the M1 antigen with the MART-1 antigen to obtain MART-1 specific TCR *in vivo*.

Applicants argue the reference do not teach all the limitations of the claims. Applicants argument is not persuasive because the combined teachings of Man and Cole teach all the limitations of the claims.

Applicants argue that the combined teachings of Man and Cole do not provide adequate guidance to obtain CTL in transgenic mice using TAA because it was not predictable at the time of filing that MART would be processed properly in the APCs of mice such that a CTL response would occur. Applicants argement is not persuasive. The reference cited by applicants teaching the difference between antigen processing in APC of mice and humans (Yewdell) is dated 1999 which is after the time of filing. Therefore, applicants have not established that at the time of filing, one of ordinary skill would have thought it unreasonable to administer a human antigen (MART) into mice and obtain adequate processing of the antigen and a CTL response.

Furthermore, despite the fact that antigens are processed differently in mouse and human APC, MART is recognized by mice as a foreign protein and still processed by the mouse APCs. Just because the antigens would be processed differently in mice and humans does not indicate the level of MART presentation in mouse APCs would not induce a CTL response. Finally, one of ordinary skill in the art would have known that human tumor antigens could be adequately processed in mice such that a CTL response would be obtained. Kuby (Immunol., 1992, W.H. Freeman and Company, page 519) taught that administering a vector encoding the human melanoma antigen p97 to mice induced a CTL response against p97 in the mice. For such a response to occur, the p97 protein was expressed by the vector, recognized by a mouse APC as foreign and processed by the APC such that an epitope of p97 is displayed on the surface in the context of an MHC molecule to a level such that the CTL response is induced. Applicants have not provided any evidence that the amount of processing of MART in mouse APCs would result in inadequate MART presentation on the mouse APC and failure to induce a CTL response. Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining adequate processing of MART in mouse APCs such that a CTL response would be induced.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER